New Drug Discovery for SMA using Patient-derived Induced Pluripotent Stem Cells

Grant Award Details

New Drug Discovery for SMA using Patient-derived Induced Pluripotent Stem Cells

Grant Type: Early Translational II

Grant Number: TR2-01844

Investigator:

Name:	John Dimos
Institution:	iPierian, Inc.
Type:	PI

Disease Focus: Neurological Disorders, Pediatrics, Spinal Muscular Atrophy

Human Stem Cell Use: iPS Cell

Award Value: $2,410,000

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Grant Application Details

Application Title: New Drug Discovery for SMA using Patient-derived Induced Pluripotent Stem Cells

Public Abstract:

Spinal muscular atrophy (SMA) is the leading genetic cause of infant death in the U.S. This devastating disease affects 1 child in every 6,000-10,000 live births, with a North American prevalence of approximately 14,000 individuals. The disease is characterized by the death of spinal cord cells called motor neurons that connect the brain to muscle. Death of these cells causes muscle weakness and atrophy, which progresses to paralysis, respiratory failure and frequently death. The three different types of SMA differ in severity and prognosis, with Type I being the most severe. SMA is caused by a genetic defect that leads to reduced levels of a single protein called SMN.

There are currently no approved therapies for the disease. The existing treatments for SMA consist of supportive care for the respiratory and nutritional deficits, for example ventilation and feeding tubes. Previous attempts to develop drugs using conventional technologies, such as cultured cancer cells or cells derived from animals have been unsuccessful. These failures are likely due the fact that previous attempts used cell types that don't reflect the disease or aren't affected by low levels of the SMN protein.

Our approach uses patient-derived motor neurons, the specific cell type that dies. We will conduct drug discovery experiments using these motor neurons to find potential therapeutics that increase the levels of the SMN protein in these diseased cells. Induced pluripotent stem cell (iPSC) technology allows us to take skin cells from patients with SMA, grow them in a dish, and turn them into motor neurons. We are conducting high-throughput screens of potential drugs with these cells to identify drug candidates that increase SMN protein levels in motor neurons derived from SMA patients. An added advantage to our approach is that we can test our drug candidates in motor neurons from many different patients, with different disease subtypes and from different ethnic backgrounds. We have generated iPSCs from many patients with SMA and we will test compounds for effectiveness against this cohort. These studies will give us an indication of the effectiveness of our compounds across patients before moving into costly and lengthy clinical trials.

If our drug candidate is successful, it could be the first effective therapeutic available for SMA. It will increase the amount of SMN protein and prevent motor neuron death. Halting the death of spinal cord motor neurons prevents the progressive weakness and muscle atrophy. We anticipate that this would prevent disability in Type III patients. For Type I and II patients, we believe such a therapy would mitigate respiratory and feeding challenges and allow lifespan increase.

The sponsoring institution has integrated iPSC-based drug discovery capabilities, ranging from stem cell line production, high throughput drug screening and medicinal chemistry. Accordingly, this institution is uniquely positioned to achieve the aims of this grant.

Statement of Benefit to California:	Spinal muscular atrophy (SMA) is the second-most common autosomal-recessive disorder and leading genetic cause of death of infants in the U.S. We estimate that there are up to 1,500 SMA patients currently living in California, with 100 new cases diagnosed in California every year. The CIRM Early Translational II Awards is intended to fund studies that will propel drug discovery forward for many devastating diseases. In keeping with this mission, we propose to leverage iPSC technology to generate disease-relevant cell types from patients themselves for a high throughput drug screen. A successful therapy for SMA would lead to significant cost savings to California's health care system, and would provide relief to families of patients with this devastating disorder. Given that there are not many successful drugs in the making for neurological diseases such as ALS, SMA, Parkinson's disease or Alzheimer's disease, our project should significantly impact drug discovery in this area by introducing iPSC technologies as a valid drug discovery and development platform. The application of iPSC-based disease modeling and drug discovery to SMA is highly innovative and represents the opportunity to establish worldwide leadership for California in this emerging field. Furthermore, the sponsoring institution will fund over 70% of the direct costs during the timeframe of this award. Accordingly, the 3:1 leverage provides great opportunity to magnify the effect of a CIRM award. Our research program will also create new, high-paying jobs in California, and will stimulate California's economy by creating new research and clinical tools. These activities will continue to strengthen California's leadership position at the forefront of the stem cell and regenerative medical revolution of the 21st century.

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